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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/472,232	12/27/1999	Jacques Dumas	BAYER-9-C1	8474

23599 7590 06/18/2004

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EXAMINER	
RAO, DEEPAK R	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 06/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/472,232	DUMAS ET AL.	
	Examiner	Art Unit	
	Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10,15,16 and 18-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10,15,16 and 18-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *122302 (page 3)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on March 30, 2004.

Claims 1-2, 4-10, 15-16 and 18-40 are pending in this application.

The following rejections are withdrawn:

The rejection under 35 U.S.C. 112, first paragraph of the previous office action is hereby withdrawn in view of the amendments and remarks showing where the amendments are supported in the specification and/or parent application.

The rejection under 35 U.S.C. 102(e) of the previous office action is hereby withdrawn in view of the amendments.

The following rejections are maintained:

Claims 1-2, 4-10, 24-25 and 30-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the claims, in the definition of M, the group "-$NR^5C(O)NR^5R^{5'}$-" is not a proper bivalent group because the second nitrogen already has satisfied permissible valencies. Further, the specification provides neither any explanation nor examples of compounds having the above specified group. (The discrepancy is found in the independent claims 1, 30 and 33).

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'one of R^5 or $R^{5'}$ are intended to be bivalent and provide the bond to L^1 '. The definitions provided for R^5 and $R^{5'}$ do **not** include any bivalent moieties, the

groups alkyl, alkenyl, etc. are conventionally known to represent monovalent substituent groups and not bivalent groups as intended by the applicants. A bivalent saturated hydrocarbon group is conventionally referred as an "alkylene" group, e.g., methylene (i.e., $-CH_2-$). The specification does provides neither any description regarding R^5 and $R^{5'}$ to be bivalent groups nor examples having a M group such as $-NR^5-C(O)-NR^5-CH_2-$. The definitions of R^5 and $R^{5'}$ are monovalent in all other situations and there is no mention any where throughout the disclosure and the claims that these can be bivalent groups, and there are no examples to support the argument that they can be bivalent. This is further evident from the other definitions of M wherein the nitrogen atom is only substituted by one R^5, see e.g., $-NR^5C(O)-$, $-C(O)NR^5-$, $-(CH_2)_mNR^5-$, etc. Accordingly, it is maintained that the above definition of M, namely "$-NR^5C(O)NR^5R^{5'}-$" is improper.

The following rejections are under new grounds:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-16, 18-23, 26-29 and 35-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of cancer of the colon, does not reasonably provide enablement for the treatment of all other diseases of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to the treatment of 'disease mediated by raf kinase' and according to the specification, the compounds are useful in the treatment of tumors and/or cancerous cell growth mediated by raf kinase, see specification page 2, lines 5-17. Further, the specification discloses several types of cancers, e.g., solid cancers, myeloid disorders, adenomas. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Further, no compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers and/or diseases mediated by raf kinase in general.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases mediated by raf kinase which includes tumors and/or cancerous cell growth.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat all types of cancers.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders embraced by the instant claims nor there are doses given for the treatment of the disorders recited. The specification provides assays (see pages 33-35) to test the compounds *in vitro* and discloses that the compounds exhibit raf kinase inhibitory properties. However, no *in vivo* test procedures or data provided for the compounds commensurate in scope of the claims and there is no disclosure regarding how the *in vitro* results correlate to *in vivo* tests. *In vivo* test procedures are provided for the cancers of the colon in mice (see page 35), however, there is no demonstrated correlation that the tests and results apply to all of the disorders embraced by the instant claims.

6) The breadth of the claims: The instant claims embrace the treatment of all diseases mediated by raf kinase. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Note: This rejection was inadvertently omitted in the previous office action.

Applicant's arguments filed in the previous responses have been fully considered but they were not deemed to be persuasive. Applicant's cited decision, *Ex parte Henning* has been reviewed, however, is not deemed to be sufficient to overcome the instant rejection. In *Henning*, the compounds were disclosed to have 5-HT_{1A} antagonistic or seratonin inhibitory activities, which are well established in the art. Further, specification disclosed that 'the compounds have anxiolytic, antidepressant, antipsychotic, neuroleptic or antihypertensive activities' which was consistent with the claim language and thus, it was ruled that the evidence of record was sufficient to meet the enablement requirements. The instant claims on the other hand are drawn to "A method for the treatment of **disease** mediated by raf kinase...." (see claim 15) and the specification discloses that the compounds are useful 'in the treatment of tumors and/or cancerous cell growth mediated by raf kinase' (see page 2, lines 9-10). The background of the

invention also provides discussion related to treatment of cancers. However, the recitation "**disease**" is understood for 'an abnormal condition that impairs normal physiological functioning' (as per Webster's) and the instant claims include diseases other than cancers and there is nothing in the specification regarding what these diseases are. Further, the test procedures and data of the specification are drawn to the inhibition of oncogenic cell growth. There is nothing on the record to enable one skilled in the art to use the compounds in the treatment of all diseases mediated by raf kinase nor the does the record identify which diseases are contemplated. The dosage regimen at pages 16 of the specification is fully considered, however, the disclosure does not provide sufficient guidance or direction towards treatment of all 'diseases' mediated by raf kinase. As submitted by the applicant, "the particular method of administration will depend on a variety of factors" (see page 16, lines 31-32) and the instant application does not provide reasonable explanation of the 'diseases mediated raf kinase' within the scope of the claims and therefore, it will be undue burden on the skilled artisan to evaluate the diseases and further the variety of factors required to adopt the dosage regimen.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The definition provided for B lists compounds as well as monovalent substituent groups. For example, diphenyl ether (i.e., Ph-O-Ph), diphenyl thioether (i.e., Ph-S-Ph), etc. are compounds *per se* and one of ordinary skill in the art would not envisage a monovalent group from these recitations. The substituent group 'pyridinylmehtylphenyl' (i.e., pyridinyl-CH_2-Ph-)

is a proper monovalent substituent properly dependent on claim 1. Thus the claim includes compounds as well as substituent groups recited for B.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 35-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Regan et al., U.S. Patent No. 6,080,763. The reference discloses pyrazolyl derivatives (see the compounds disclosed in Table 1, col. 35-38 wherein the 5-membered ring is A) and the reference discloses that the compounds have therapeutic effect on various diseases of mammal through the inhibitory activity on variety of inflammatory cytokines such as IL-1, IFNγ, etc. which diseases include oncological diseases (see col. 3); multiple myeloma (see col. 5), etc. The reference also indicates that 'cytokines stimulate proliferation' and the compounds of the invention inhibit the release of cytokines. Further, the reference teaches that IFNγ is implicated in a number of diseases, including cancers, and cancers generally include any proliferation of cells, which results in unregulated growth. The instant claims read on the prior art taught therapeutic effect because the instant claims are drawn to administration of the compounds that are structurally identical to those disclosed in the reference, in same dosages, to the same population. Therefore, the reference inherently teaches the claimed method of treatment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-10, 15-16 and 18-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Regan et al., U.S. Patent No. 6,080,763. The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See formula (I) in col. 6 wherein the heteroaryl ring represented by ABDEG is a pyrazolyl ring as shown in the examples; Y is –NH-; X is O; and R5 is phenyl, naphthyl, etc. which is further substituted by one to five substituents which substituent list includes alkyl, halo, cyano, phenyloxy, naphthyloxy, phenylamino, naphthylamino, etc. Further, the reference discloses many examples, see Table 1, wherein Het is A; R_3 is optionally substituted phenyl and R_5 is optionally substituted phenyl. The compounds are taught to be useful as pharmaceutical therapeutic agents, see the abstract. Claims 35-38 are anticipated by the reference as indicated above in the rejection under 35 U.S.C.

102. The remaining claims differ from the reference by reciting a specific species and/or a more limited genus than the reference. The reference does not expressly disclose a compound having a bridged substituent group such as a phenyloxy, however, the reference teaches the equivalence of the substituents groups as they are disclosed to be alternative substituents on the cyclic groups. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Contrary to applicant's arguments, the Provisional Application 60/064,102 provides sufficient suggestion of an aryloxy or heteroaryloxy, arylamino, heteroarylamino groups to be a substituent on R_5, see page 6 of the application, which provides sufficient motivation to one of ordinary skill in the art to substitute the R_5 aryl group with any of the substituents disclosed in the examples including those generically taught as they are all taught to be equivalent.

Note: Applicant's attention is directed to U.S. Patent 6,319,921 which while not a competent reference against the instant claims, discloses and claims subject matter that is substantially similar to that claimed herein. Unless applicants can demonstrate that the claims are patentably distinct from the claims in this US patent, the only way to overcome these patents is by way of interference proceedings or removal of the conflicting subject matter. See MPEP § 2306.

One reference in page 3 of the IDS filed on December 23, 2002 was not initialed, which is now completed and a copy is enclosed for applicant's records.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

June 15, 2004